Chemotherapy-induced Gonadotoxicity

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Fertility preservation for women with malignancy has recently gained importance for the following reasons. First, malignant diseases are not rare in women of reproductive age [1]. Second, progress in cancer treatment has markedly improved the survival rates of these patients. Third, conservative surgery in the management of cancers of the female reproductive organs (organ-preserving surgery) has become more acceptable. Fourth, the use of preoperative or postoperative radiotherapy or chemotherapy might directly or indirectly affect ovarian function, although the direct mechanisms of chemotherapy-induced ovarian failure are poorly understood. Visualization of end *in vivo* chemotherapeutic damage to human oocytes is practical at autopsy or after the completion of treatment [2]. Fifth, because of the recent trend toward delayed pregnancy [3–6], an increasing number of patients may request preservation of future fertility. There is still no consensus on the optimal therapeutic approach with which to manage patients with cancer who wish to preserve their fertility. Furthermore, the number of women diagnosed with cancer-related diseases and who wish to maintain their future reproductive function is increasing. Therefore, this raises the question, how can the cytotoxicity of therapy on the gonads of these female cancer patients be reduced?

In fact, ovarian damage and failure is an important and, unfortunately, common long-term side effect of curative chemotherapy [2]. Sterilization and early menopause in young female adults have a high-level impact on patient self-esteem and quality of life, as in the case reported by Lee and Pan in this issue [7]. The patient lost her interest in sexual activity when she was diagnosed with cancer, even though she was informed that she had been cured by chemotherapy. Unfortunately, the prospect of ovarian failure and impaired fertility after antineoplastic therapy is a difficult topic for patients and clinicians to deal with because of the lack of good prognostic information. The frequency of ovarian failure varies with factors such as the type, dose, duration of chemotherapy treatment, and age of the patient [2]. There are currently no reliable estimates for the magnitude of risk associated with these parameters, because acute ovarian failure can occur during or shortly after the completion of irradiation or chemotherapy and may be transient or permanent. In contrast, premature ovarian failure or premature menopause typically manifests after a post-treatment return of regular menses with subsequent loss of ovarian function before the age of 40 years [8]. Therefore, any agent that might provide potential benefits in protecting the ovarian function of women with cancer who were treated with cytotoxic drugs or radiation is welcome. We wish to update recent knowledge regarding this serious topic.

First, modern techniques to prevent treatment-induced ovarian ablation include better shielding of the ovaries from the damaging effects of radiation. This can be accomplished by implementing transposition procedures to move the ovaries outside of the area at risk [8]. Second, embryo cryopreservation is an established clinical procedure after *in vitro* fertilization and is currently the only widely available option for fertility preservation in female patients who need chemotherapy or radiotherapy [1]. Third, oocyte cryopreservation is an experimental option for female fertility preservation that can be offered to unmarried cancer patients with no male partner or to those who do not wish to use a sperm donor [1]. Fourth, unlike embryo or oocyte cryopreservation, hundreds of primordial follicles containing immature oocytes may be cryopreserved without the need for ovarian stimulation and the resulting delay in initiating cancer treatment. Ovarian cryopreservation and transplantation is an exciting but still experimental possibility for fertility preservation in women. Fifth, the use of pharmacologic prevention, e.g. gonadotropin-releasing hormone (GnRH) agonist as a co-treatment for

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chemotherapy, is still in the experimental stage. Compared with GnRH, GnRH agonists have a longer half-life and elicit prolonged continuous activation of the GnRH receptor. Downregulation of the GnRH receptor results in a decreased level of gonadotropin and suppressed production of ovarian hormones [9]. This hypothesis was based on the initial reports that erroneously concluded that pediatric patients were immune to the gonadal-damaging effects of chemotherapy [10]. GnRH agonist co-treatment for the prevention of chemotherapy-induced gonadotoxicity should only be offered to patients after obtaining informed consent from an institutional review board-approved investigational protocol, because the effectiveness of GnRH agonists as fertility-preserving agents is still debatable [10,11]. A thorough literature search has found conflicting data regarding the effectiveness of GnRH agonist co-treatment in protecting the ovary from the damage of chemotherapy [12,13].

Based on the report by Pan and Lee [7], we should take more care with and pay more attention to younger patients with cancer who wish to preserve their future fertility, even though they can be successfully cured by multimodal antineoplastic treatments.

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